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DAR-901 vaccine for the prevention of infection with *Mycobacterium tuberculosis* among BCG-immunized adolescents in Tanzania: A randomized controlled, double-blind phase 2b trial

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ABSTRACT

Background: SRL172 prevented disease due to *Mycobacterium tuberculosis* in a Phase 3 trial. DAR-901 represents a scalable manufacturing process for SRL172. We sought to determine if DAR-901 would prevent infection with *M. tuberculosis* among BCG-primed adolescents age 13–15 years in Tanzania.
Methods: Adolescents with a negative T- SPOT.TB[R] interferon gamma release assay (IGRA) were randomized 1:1 to three intradermal injections of DAR-901 or saline placebo at 0, 2 and 4 months. Repeat IGRAs were performed at 2 months, and at 1, 2, and 3 years. The primary efficacy outcome was time to new TB infection (IGRA conversion to positive); the secondary outcome was time to persistent TB infection (IGRA conversion with repeat positive IGRA).
Results: Among 936 participants screened 667 were eligible and randomized to their first dose of vaccine or placebo (safety cohort). At 2 months, 625 participants remained IGRA-negative and were scheduled for the additional two doses (efficacy cohort). DAR-901 was safe and well-tolerated. One DAR-901 recipient developed a vaccine site abscess. Neither the primary nor secondary endpoints differed between the two treatment arms (p = 0.90 and p = 0.20, respectively). DAR-901 IGRA converters had median responses to ESAT-6 of 50.1 spot-forming cells (SFCs) vs. 19.6 SFCs in placebo IGRA converters (p = 0.03).
Conclusions: A three-dose series of 1 mg DAR-901 was safe and well-tolerated but did not prevent initial or persistent IGRA conversion. DAR-901 recipients with IGRA conversion demonstrated enhanced immune responses to ESAT-6. Since protection against disease may require different immunologic responses than protection against infection a trial of DAR-901 to prevent TB disease is warranted.
Trial Registration. The trial is registered at ClinicalTrials.gov as NCT02712424.

1. Introduction

Tuberculosis (TB) is the leading infectious disease cause of death in the world [1]. The World Health Organization (WHO) has targeted elimination of tuberculosis by 2030, an objective that will require development of a more effective preventive vaccine strategy. The only licensed vaccine against tuberculosis, Bacille Calmette-Guerin (BCG), is effective when given as a priming vaccine at birth, but activity wanes after 15–20 years [2]. Both improved priming vaccines and new booster vaccines are in development but modelling indicates that an adolescent and adult booster would have a greater impact on the epidemic than an improved priming vaccine over the initial several decades [3–6]. Preferred Product Characteristics (PPCs) defined by WHO for a new vaccine include efficacy of at least 50%, as well as safety and efficacy in all of the following groups: persons with and without prior infec-

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tion with *Mycobacterium tuberculosis*, and persons with HIV infection [7].

SRL172, an inactivated whole cell non-tuberculous mycobacterial vaccine, was shown to be safe and immunogenic in HIV-uninfected and HIV-infected participants [8]. In a subsequent Phase 3 trial, SRL172 was administered as a 5- dose booster to BCG-primed, HIV-infected patients in Tanzania and showed protection against TB disease in those with and without prior infection with *M. tuberculosis* [9]. DAR-901 is the product of a new, scalable manufacturing method for SRL172. It has been shown to be effective as a BCG booster in preventing TB disease in pre-clinical studies [10]. A Phase 1 trial in the United States showed that a three-dose series of DAR-901 was safe and immunogenic in BCG-primed adults with and without prior infection with *M. tuberculosis* and safe in patients with HIV infection [11,12].

In the present Phase 2b study, we sought to determine whether DAR-901 was safe and effective in preventing initial or persistent infection with *M. tuberculosis* among BCG-primed adolescents in Tanzania.

2. Methods

2.1. Study design and participants

In this randomized, double-blind, placebo-controlled study we recruited and screened healthy adolescents aged 13–15 years from 16 secondary schools in Dar es Salaam, Tanzania between April and October 2016 and administered study treatment (DAR-901 or saline placebo) from April 2016 to March 2017. Follow-up was continued for up to three years through December 2019. We obtained written informed assent from all participants and informed consent from their parents or guardians. Eligibility requirements included a BCG vaccine scar or provision of an immunization card indicating prior BCG immunization, a negative T-SPOT.TB^{R} (Oxford Immunotec, Oxford, UK) interferon gamma (IFNγ) release assay (IGRA) for infection with *M. tuberculosis*, a normal complete blood count, normal vital signs, and no history of TB or chronic illness. All female participants were required to have a negative urine pregnancy test (Laborex HCG, Clarity, Milan, Italy) prior to each immunization.

Ethical approval for the study was obtained from the Dartmouth Committee for the Protection of Human Participants in the US; the National Institute for Medical Research, Tanzania, and the Muhimbili University of Health and Allied Sciences (MUHAS) Research Ethics Committee. Regulatory approval was obtained from Tanzania Medicines and Medical Devices Authority. Permission to conduct the study within schools was granted by the Ministry of Education. The study was conducted in accordance to principles of International Community of Harmonization and Good clinical practice (ICH-GCP). An independent Data and Safety Monitoring Board monitored patient safety.

2.2. Investigational product

DAR-901 is an inactivated whole cell non-tuberculous mycobacterial vaccine produced from the same Master Cell Bank used for production of SRL172. Whereas SRL172 was agar-grown, DAR-901 was prepared from broth-grown organisms, an approach more appropriate for commercial scale. The vaccine used in the present trial (Lot# 12-107F-001) was manufactured by Aeras (Rockville, MD) in December 2012. Bulk drug substance was diluted to a concentration of 10 mg/mL and then 0.3 mL aliquots dispensed in glass vials. Samples of the lot underwent standard toxicity and potency testing every 6 months during the trial. All tests were in the acceptable range including potency based on an IL-12 release assay. Pre-clinical studies in mice using the final drug product demonstrated a dose-dependent immune response and provided protection against TB challenge that was superior to BCG [10].

2.3. Randomization and masking

Eligible adolescents were randomized 1:1 to DAR-901 or saline placebo in block sizes of four. DAR-901 was provided in 2 mL dose vials containing a 0.3 mL suspension of heat-inactivated organisms. Saline placebo was obtained as Sterile Saline for Injection, USP. Computer-generated randomization was performed centrally and provided to the study pharmacist who filled a tuberculin syringe to 0.1 mL with vaccine (1 mg) or placebo; both were colorless. A blinded study nurse administered the intradermal injection over the deltoid, alternating between left and right arms.

2.4. Procedures

The three doses of vaccine or placebo were administered at baseline, at 2 months, and 4 months. The T-SPOT.TB^{R} IGRA was performed at screening, prior to dose 2, and at follow-up visits at 1, 2, and 3 years. Participants with IGRA conversion to positive had a repeat IGRA performed at $\geq$3 months. A complete blood count was performed before each dose of vaccine or placebo and at 2 and 3 years. Safety visits for injection site examination were conducted 7 days after each immunization. Paxgene^{R} tubes were obtained 7 days after Dose 3 for future analysis of RNA expression.

Vital signs were taken before and 30 min after and 7 days after each dose of study treatment. At the 7-day safety visits, the injection site was inspected and erythema and induration measured. Participants were questioned at each visit regarding both non-solicited adverse events (AEs) as well as potential vaccine-related systemic and local AEs including fever, pain, ulceration or erosion at the injection site. Injection site reactions, abnormal laboratory values, and all other adverse events were graded based on guidelines for vaccine trials from the United States Food and Drug Administration [13].

T-SPOT.TB^{R} IGRA assays were performed according to manufacturer's instructions. Spot counts were enumerated by a blinded study technician based on manual reading of wells in the 96-well microtiter plate using a hand lens and categorized as negative, positive, borderline, or invalid for the per protocol study endpoints. The manual count limit was 20 spot forming units (SFCs). Study plates were subsequently shipped to Oxford Immunotec (Oxford, UK) to allow quantitative blinded reading (automated, with manual confirmation), including responses with >20 SFCs.

2.5. Populations and outcomes

The safety population was defined as all participants who received at least one dose of study treatment (vaccine or placebo). The DAR-901 safety population represented all participants who received at least one dose of DAR-901, whether as assigned or in error. The placebo safety population represented all participants who received only saline, whether as assigned or in error.

The Intent to Treat (ITT) efficacy population represented all participants who had negative IGRA results at both screening and prior to Dose 2; participants with positive, borderline or invalid results were excluded. New TB infection was defined as conversion from IGRA-negative at baseline and 2 months to IGRA-positive at any subsequent visit. The subpopulation of persistent TB infection was defined as participants with new TB infection plus a subsequent repeat positive IGRA at $\geq$3 months (even if there was an intervening negative or borderline result). The primary trial endpoint was time to initial IGRA conversion for subjects with new

TB infection. The secondary trial endpoint was time to initial IGRA conversion for subjects with persistent TB infection.

Participants with IGRA-conversion were managed as per Tanzanian guidelines which do not recommend isoniazid or other preventive treatment for tuberculosis infection in healthy adolescents. IGRA-positive participants were evaluated for symptoms of active tuberculosis using the Tanzanian TB Screening Questionnaire (TSQ) [14]. Participants with positive TSQ responses were referred to National Tuberculosis and Leprosy Program (NTLP) clinics for evaluation and treatment. All participants treated for TB disease were reviewed by a panel of three experts blinded to trial treatment assignment and to IGRA results. A consensus opinion based on review of all available clinical, radiologic and microbiologic criteria was required to categorize cases as confirmed pulmonary TB, confirmed extrapulmonary TB or not TB (formal categories were not defined).

Sample size calculations were based on an annual IGRA conversion rate of 7% as observed in prospective studies of South African adolescents [15] and estimated that 650 participants were needed to detect 50% vaccine efficacy with 80% power and 5% loss to follow-up per year. The study was designed as a 2-year trial with an estimated 67 primary endpoints. At 2 years, 29 endpoints had been observed; consequently, the trial was extended an additional year. The trial could not be extended further since the school-based cohort had graduated by 3 years and moved to diverse locations throughout Tanzania.

Solicited and unsolicited AEs were classified by the Medical Dictionary for Regulatory Activities (MeDRA)-preferred term and compared between treatment groups. Injection site reactions were deemed related to immunization. The blinded Principal Investigator assessed adverse events for their relationship to immunization. Safety laboratory studies with values outside pre-defined reference ranges were assessed for clinical significance.

2.6. Statistical analysis

The primary trial endpoint was time to new TB infection using the intention-to-treat (ITT) population, subject to right censoring for participants lost to follow-up. The proportion of participants converting over time was calculated using the Kaplan-Meier statistic. To account for interval censoring in the capture of IGRA conversion, we applied methods for discrete time-to-events. The primary test statistic was a log-rank test comparing the two study arms (ITT). An estimate of vaccine efficacy was calculated as the hazard ratio comparing vaccine to control using Cox's proportional hazards model. Point and interval estimate (95% confidence level) were calculated.

The secondary endpoint was time to persistent new TB infection as defined above and analyzed using the same methods as detailed for the primary endpoint. Although the rate of active TB (pulmonary and extra-pulmonary) was expected to be low, it was analyzed as an exploratory endpoint. For all analyses, we assigned a P-value < 0.05 as the cutoff for statistical significance.

Data management and statistical analysis were provided by a contract research organization (Axiom Real Time Metrics, Toronto, Canada) and the study statistician.

The trial is registered with ClinicalTrials.gov as NCT02712424.

2.7. Role of the funding source

The Dartmouth and MUHAS study teams were involved in the study design, interpretation of data and writing the report. The corresponding and senior authors had access to all data and had final responsibility for data analysis and writing the study report. Trial funders had no role in study design, data collection, data analysis, data interpretation or writing the report.

3. Results

3.1. Trial participants

Of the 936 adolescents screened from 16 schools in Dar es Salaam, 667 were randomized and all received at least one dose of study treatment. Among the volunteers ineligible at screening, 164 were not IGRA negative at baseline (146 positive, 17 border line, one invalid). All participants were African; baseline characteristics of study participants did not differ between the two treatment groups (Table 1). IGRA testing prior to the second dose of study treatment scheduled at two months identified 20 participants who had converted to IGRA-positive (7 DAR-901, 13 placebo, p = 0.19) and were ineligible for further immunization. The ITT efficacy cohort consisted of the 625 participants (315 DAR-901, 310 placebo) who attended the visit for dose 2 and remained IGRA negative (Fig. 1). Screening visits began on April 6, 2016, the first immunization was administered on April 27, 2016, and the last study visit occurred on December 20, 2019. At the three-year visit, a total of 66 (11%) participants had been lost to follow-up.

3.2. Safety

Adverse events occurred in 126 (38%) DAR-901 recipients and 142 (42%) placebo recipients in the safety cohort (p = 0.98) with similar patterns in both treatment groups. Serious adverse events occurred among six (2%) DAR-901 recipients and three (1%) placebo recipients (p = 0.33). No serious adverse events were judged to be related to study treatment. Shifts in values of hemoglobin, hematocrit, white blood count, and platelet counts were similar in the two treatment groups.

At the 7-day post-immunization visit, induration at the injection site was measured among DAR-901 recipients in the safety population with the following frequency for the three doses: 62%, 59% and 62%. Median induration was 5 mm after each of the three

Table 1
Baseline characteristics of study participants (efficacy cohort).

	Saline Control (N = 310)	DAR-901 (N = 315)	P-Value
Sex			0.27
Male	141 (45.5)	123 (39.0)	
Female	169 (54.5)	192 (61.0)	
Age (Years)			0.35
N	310	315	
Mean (SD)	14.2 (0.75)	14.1 (0.76)	
Median	14.0	14.0	
Min, Max	12, 17	12, 15	
BMI (kg/m^2)			0.19
N	245	252	
Mean (SD)	19.74 (3.69)	20.19 (3.67)	
Median	18.80	19.40	
Min, Max	12.5, 34.7	14.2, 35.4	
Hemoglobin (g/dL)			0.33
N	310	315	
Mean (SD)	12.7 (1.30)	12.6 (1.25)	
Median	12.7	12.6	
Min, Max	9, 24	9, 21	
White Blood Count (K/uL)			0.87
N	310	315	
Mean (SD)	6.0 (1.73)	5.9 (1.41)	
Median	5.7	5.9	
Min, Max	3, 17	3, 11	
Platelets (K/mL)			0.63
N	310	315	
Mean (SD)	312.7 (133.5)	317.2 (101.8)	
Median	298.0	306.0	
Min, Max	88, 1914	115, 1017	

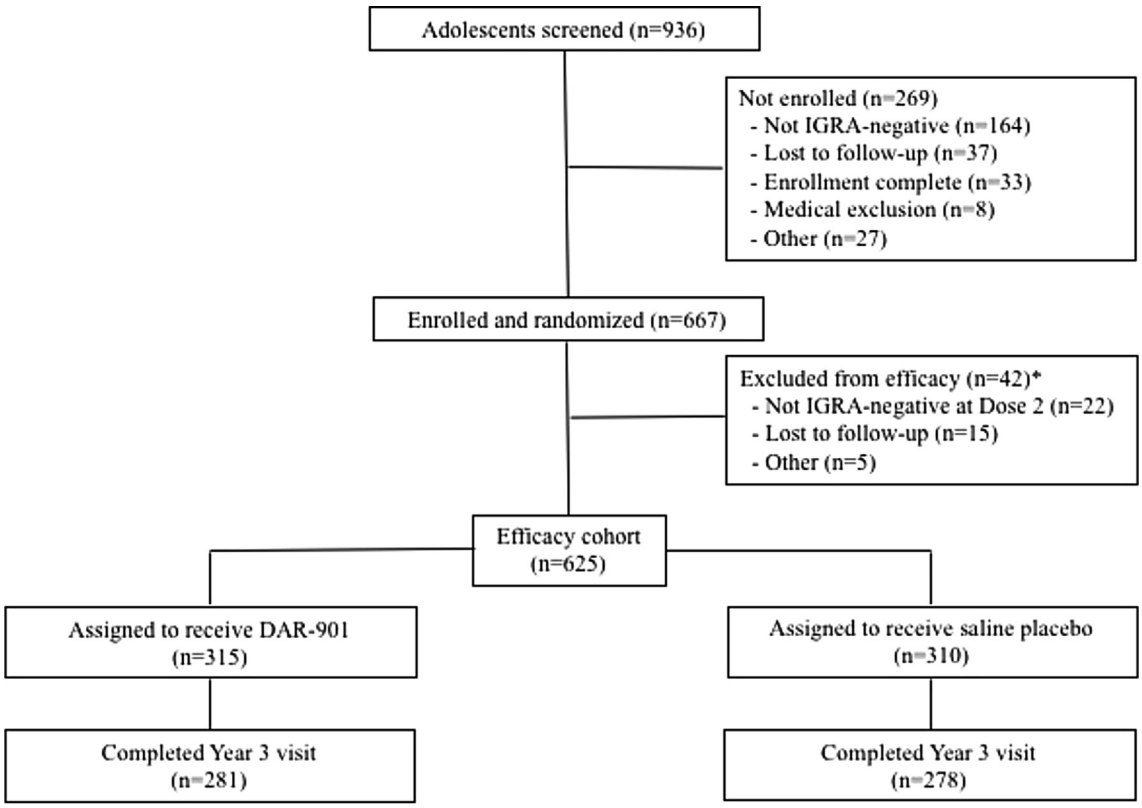

Fig. 1. Consort diagram.

doses (range 1–25 mm). DAR-901 recipients reported the following symptoms at the 7-day post-immunization visit for the three doses respectively: pain at the injection site: three (1%), 12 (4%), and seven (3%); fever: one (0.3%), two (1%), and seven (3%); and ulceration or erosion: zero (0%) at all doses. Placebo recipients reported the following symptoms at the 7-day post immunization visit for the three doses respectively: pain at the injection site: one (<1%), one (<1%), and one (<1%); fever: zero (0%), zero (0%), and one (<1%); and ulceration or erosion: zero (0%) at all doses. One DAR-901 recipient (0.03%) developed an injection site abscess 3 weeks after dose 3. The abscess drained spontaneously and responded to antibiotic treatment.

3.3. Efficacy

New TB infection (initial conversion to IGRA-positive) was observed in 19 DAR-901 recipients and 18 placebo recipients in the ITT cohort (Table 2). The primary endpoint of time to new TB infection did not differ between the two treatment groups (p = 0.89, Fig. 2). Overall, among 37 participants with IGRA-conversion, 35 (94.6%) had at least 1 subsequent IGRA (median, 2), including 20 in whom all subsequent tests were negative, and 15 with at least one subsequent positive. Among those 15 subjects with persistent TB infection 10 received DAR-901 and five received placebo. The secondary endpoint of time to persistent TB infection did not differ between the two treatment groups (p = 0.20; Figure not shown).

The exploratory endpoint of active TB was reached in two participants in the DAR-901 arm (one with prior positive IGRA, one persistent negative IGRA) and two participants in the placebo arm (both with prior negative IGRAs; one conversion to positive IGRA one month after diagnosis of Pott's disease). Among DAR-901 recipients there was no relationship between the presence of any induration 7 days after immunization and risk of TB infection or induration <5 mm vs ≥5 mm and risk of TB infection (data not shown).

Results of T-spot IGRAs among participants meeting a study endpoint based on quantitative T-spot readings are shown in Table 3. At the time of IGRA conversion (first positive IGRA by manufacturer's definitions) participants who received DAR-901 had significantly higher responses to ESAT-6 (p = 0.03) and a trend toward higher responses to CFP-10 (p = 0.14) compared to participants who received placebo. Spot forming cell (SFC) values for ESAT-6 and CFP-10 at the time of IGRA conversion among DAR-

Table 2
Vaccine efficacy based on number (N) of primary or secondary endpoints.

Endpoint	DAR 901 (N = 314)	Saline (N = 310)	Hazard Ratio (95% CI)	P-Value
1. New TB infection (N)	19	18	0.9679 (0.8228, 1.1385)	0.69
2. Persistent new TB infection (N)	10	5	0.9559 (0.8151, 1.1211)	0.58

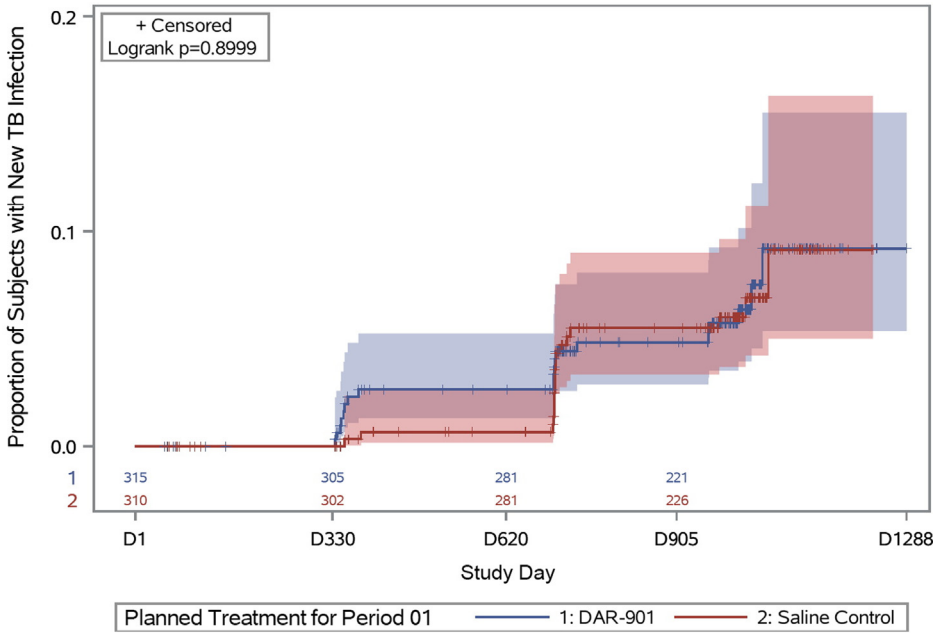

Fig. 2. Time to event for new IGRA conversion among DAR-901 vs placebo recipients.

Table 3
IGRA Spot Forming Cells (SFCs) at the time of first positive IGRA among participants reaching a primary endpoint versus participants who were IGRA positive at baseline screening.

Antigen Endpoint	1. DAR New TB infection (N = 16)	2. PLA New TB infection (N = 13)	P 1 v 2	3. Baseline IGRA positive (N = 143)	P 1 v 3	P 2 v 3
ESAT-6	50.1	19.6	0.03	44.0	0.75	0.03
CFP-10	38.1	25.5	0.14	53.2	0.50	0.04
PHA	405	392	0.71	241	0.002	0.0001

DAR = DAR-901; ESAT-6 = TB early secreted antigen – 6; CFP-10 = TB culture filtrate protein – 10; PHA = phytohemagglutinin; PLA = saline placebo.
Values represent median counts of Spot Forming Cells (SFCs); P-values calculated with non-parametric Mann-Whitney *U* test.
N represents the number of participants with results available from quantitative readings and qualifying as an endpoint by quantitative results.

901 recipients were comparable to those among participants who were IGRA positive at baseline and had been infected for unknown periods of time without developing active TB. In contrast, SFC values at the time of IGRA conversion among placebo recipients were significantly lower than SFC values among participants who were IGRA positive at baseline (Table 3).

DAR-901 recipients who remained IGRA negative had low level SFCs to both ESAT-6 and CFP comparable to placebo recipients who remained IGRA negative. PHA values were significantly higher for participants reaching either endpoint compared to participants with baseline positive IGRA results.

4. Discussion

A three-dose series of 1 mg DAR-901 was safe and well-tolerated in IGRA-negative, BCG-immunized adolescents in Tanzania. Adolescents are a priority target group for booster immunization since the efficacy of BCG begins to wane at 15–20 years [2]. Thus, the safety demonstrated in this age group adds to the accumulating evidence supporting the potential for this inactivated whole cell non-tuberculous mycobacterial vaccine to serve as a BCG booster: superior protection to BCG in an animal model [10], safety and immunogenicity in healthy and HIV-infected participants [8,9,11,12,16], 39% efficacy in preventing TB disease in HIV-infected participants [9], and efficacy in both TB-infected and TB-uninfected participants [9]. Except for the efficacy target of 50%, these trials align DAR-901 with the World Health Organization Preferred Product Characteristics for investigational TB vaccines [7].

Although the number of IGRA conversions fell below our target for detecting 50% vaccine efficacy the failure of DAR-901 to show even a trend toward prevention of IGRA conversion indicates that, as administered, three doses of this formulation is not effective in preventing infection with *M. tuberculosis* as assessed by IGRA. This was unexpected given the efficacy of DAR-901 against disease in a pre-clinical model [10] the efficacy of the parent SRL172 strain against TB disease [9], and the comparable immunogenicity of SRL172 and DAR-901 [11,17].

Quantitative or qualitative differences between DAR-901 used in the present prevention of infection trial and SRL172 used in the prior prevention of disease trial may have contributed to differences in outcomes. For both preparations, the dose administered was 1 mg. However, for SRL172 the dose was reported to represent 1 x10^9 colony-forming-units (CFUs) based on a manual assay, whereas the 1 mg dose of DAR-901 in the present trial represents 7 $\times$ 10^6 organisms measured by qPCR of bacterial DNA [9,11]. In clinical trials, SRL172 was administered in a 5-dose rather than the present 3-dose series, although a 3-dose series of DAR-901 has been shown to have comparable immunogenicity to 5 doses of SRL172 [9,17]. In pre-clinical studies, BCG-primed mice admin-

istered a 3-dose series of DAR-901 showed a dose-dependent immune response and a dose of 0.3 mg DAR-901 provided optimal and superior protection to BCG in a challenge study [10]. We have not studied human immune responses to DAR-901 at doses other than 1 mg. DAR-901 was manufactured using organisms grown in broth, whereas for SRL172 growth on agar was used. Growth in broth is required for cost-effective large-scale production, but might result in a different antigenic profile compared with growth in agar.

Although differences between DAR-901 and SRL172 vaccine formulations may have impacted the outcome of the present trial, vaccines may prevent disease without prevention of infection [18]. Conversely a vaccine might prevent infection without preventing disease. A BCG booster was recently reported to reduce the risk of TB infection, defined as persistent IGRA conversion, among healthy IGRA negative-adolescents in South Africa [19]. However, two large prospective trials have demonstrated that BCG boosters do not reduce the risk of TB disease [20,21]. In the Malawi trial there was no difference in the rate of TB disease among BCG-primed adults in the BCG booster vs. placebo groups with over 23,000 participants in each arm [21]. In the Brazil trial there was no difference in the rate of TB disease among BCG-primed children age 7–14 in the BCG booster vs. placebo groups with over 90,000 participants in each arm [20].

Additional findings in the present trial suggest that there was a biologic response to DAR-901. There was an unexpected trend toward more cases of persistent IGRA conversion in DAR-901 recipients than placebo recipients. In addition, DAR-901 recipients who developed IGRA conversion had significantly higher IFNγ responses to ESAT-6 than placebo recipients. Of particular note, the ESAT-6 responses in DAR-901 converters were comparable to those observed in participants who were IGRA positive at baseline and had not progressed to active TB disease. Epidemiologic studies have demonstrated that prevalent TB infection has a lower risk of progression to TB disease than incident TB infection [22–25], suggesting that that prevalent IGRA-positives have already passed the period with the highest risk of progression and may have established immune control [22–25]. We hypothesize that the robust ESAT-6 responses observed in DAR-901 recipients with IGRA-conversion are part of a broader polyantigenic response to a whole-cell vaccine that protects against progression to TB disease. This hypothesis will be explored further in a Phase 3 prevention of disease trial with DAR-901.

IFNγ is a cytokine produced by activated T cells that are required for protection against tuberculosis. IGRA assays have proven useful for identifying and treating persons with latent tuberculosis, including recent household contacts [26]. However, as others have suggested, that does not establish that IGRA-conversion will be a reliable endpoint for predicting protection against the risk of TB disease in vaccine trials [27]. The increased intensity and persistence of IGRA responses in DAR-901 recipients suggests caution in assuming that vaccine-induced protection against TB infection defined as IGRA-conversion should replace the current standard for licensure, vaccine-induced protection against TB disease defined by clinical and microbiologic criteria.

There are several limitations of the present trial. The observed rate of IGRA conversion in Tanzanian adolescents was lower than the rate in South African adolescents that was used for the sample size calculation. Although the study was consequently underpowered, the failure to show any difference from placebo establishes that this regimen does not prevent IGRA conversion. In the Phase 1 trial of DAR-901 we demonstrated antibody and diverse cytokine responses to both tuberculous and non-tuberculous antigens [11,12]. However, those assays were not included in the present trial of this polyantigenic vaccine. The responses to ESAT-6, a single protein, observed in the present trial provide only a limited indication of the responses that are expected with a polyantigenic vaccine that shares thousands of antigens with other mycobacteria. HIV testing was not performed for healthy adolescents in this trial because they are a low risk group in Tanzania [28] and discussion with community advisory groups indicated that routine testing would have severely compromised recruitment. Per-protocol inquiry about concomitant medications identified one participant with new HIV infection late in the trial.

In conclusion the present trial has confirmed the safety and tolerability of a 3-dose series of DAR-901 in a BCG-primed adolescent population living in a TB-endemic country. Enhanced ESAT-6 responses among DAR-901 recipients with IGRA-conversion suggests a possible correlate for prevention of TB disease previously observed with a polyantigenic whole cell vaccine prepared from the same Master Cell Bank. The fact that DAR-901 failed to prevent TB infection (IGRA conversion) while the parent SRL172 vaccine prevented TB disease raises the possibility that prevention of infection trials may not reliably predict vaccine efficacy against TB disease. The efficacy of DAR-901 in the prevention of TB disease will require confirmation a Phase 3 trial.

5. Contributors

CFvR, RDA, KP, PM, TM, KN and MA, designed the study. KP, MM, PM, CFvR, MA, JD, IM, AM, ST, WWA and RC conducted the study. CR, CB-K, TM, WW-A, LVA, and CRH assisted with data analysis. CFvR, RDA and PM wrote the manuscript and all authors contributed to review and approval of the manuscript.

6. Data sharing

De-identified individual participant data that underlie the results reported in this Article will be available upon request on the FigShare platform after publication. The full study protocol and statistical analysis plan are available on FigShare.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.vaccine.2020.09.055.

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